REMARKS

The Examiner's Office Action indicated that it was a response to Paper #13, filed 24 June 2003. Claim 19 had been cancelled. Applicant's amendments to claim 1-3,7-9, 12-13, and 18 were acknowledged. Claim 6, 10, 11 and 20-22 were rejoined. Claims 1-18 and 20-22 were examined. The Applicants thank Examiner Snedden for the courtesies extended in the personal interview of September 10, 2003. Attached is a Record of the Substance of an Interview.

Claims 1, 5, 7-9, 12-14, 17-19 were rejected under 35 USC §102(b) as being fully anticipated by Coutsoudis, Cherouny et al., Barnett et al., Japanese Patent 6,019,7669 or Buhimschi .

Further Claims 1, 2, 4, 5, 7-9, 11-19 were rejected under 35 USC §103 as being unpatentable over Buhimschi et al. in view of Cherouny et al.

Allowable Claims

The Examiner indicated that Claims 6, 10, 20, 21, and 22 were in a condition for allowance. Thus, the five allowable claims have been rewritten in proper independent and dependent formats and should be still allowable.

Rejections Under §102 and §103

The Applicants' strongly disagree with the Examiner's 102 and 103 rejection basis. However, the Applicant's believe that the current amendments to the rejected claims clarify the population of pregnant animals to those "experiencing excess free radical generation."

The §103 basis for rejecting Claims 1, 2, 4, 5, 7-9 and 11-19 relies upon one of the instant inventor's own publication (Buhimschi et al. (1999)). This publication may not be considered as prior art since it was published for the first time to participants at the Society for Maternal Fetal Medicine on January 21, 1999. The present Application claims priority from provisional application USSN 60/176,676, filed January 18, 2000, i.e., less than one year from the publication date. Attached is a Declaration under Rule 131 supporting

the Inventor's assertion. Therefore the Examiner's §103 basis of rejection of claims 1, 2, 4, 5, 7-9, and 11-19 has been overcome.

Regarding the Examiner's §102 rejection, the Applicants present the following arguments about each §102 reference in light of the clarifying amendment to the claims:

1. Coutsoudis:

The examiner states that Coutsoudis et al teach provitamin A or beta-carotene supplementation has the potential to reduce the incidence of preterm birth. He also states that the supplementation was given to women likely to suffer from pre-term labor and thus the reference anticipates our invention. Upon review of the publication by Coutsoudis et al (AIDS 1999) we respectfully disagree with the examiner for the following reasons:

a. The population enrolled by Coutsoudis et al. was pregnant HIV-infected women in Durban South Africa, many with low vitamin A levels. In point, the Coutsoudis study was designed to evaluate the effect of supplementation with either vitamin A or beta-carotene on HIV mother-to-child transmission, and not the effect of these compounds on preterm birth per se. The authors themselves describe the enrolled population as being nutritional deficient and with high risk of anemia:

> "In Durban, anemia in seropositive pregnant women was shown to be a major risk factor for mother-to-child transmission of HIV-1; it is not known whether this is a primary nutritional intake problem or whether this is a primary nutritional intake problem or whether it reflects HIV disease activity. Vitamin A supplements have been shown to play a role in improving hemoglobin levels and indices of iron metabolism. Based on the results of this study maternal supplements of vitamin A may be helpful to pregnant women at risk of preterm delivery."

Our reading of the Coutsoudis teaching is that in nutritionally deficient women or in women with anemia correction of the vitamin A deficiency and or their anemia improves their overall health, and one benefit from improved health **may** be a modest decrease in the

preterm delivery rate. **This teaching cannot be generalized to the general population of women at risk of preterm delivery, as the vast majority of them are not nutritionally deficient or anemic. In fact, it is well known that vitamin A fortification, which was introduced Western society to prevent neural tube defects a decade ago has had no effect on the rate of preterm delivery in the general population.** The preterm delivery rate has actually risen in the US over the past decade. (Jams JD. Prediction and early detection of preterm labor. Obstet Gynecol. 2003 Feb; 101(2):402-12.) As recently reviewed by the WHO (World Health Organization), "No specific nutrient supplementation was identified for reducing preterm delivery." (Villar .J Merialdi Al, Gulmezoglu AM, Abalos F, Carroli G, Kulier R, de Onis M. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. J Nutr. 2003 May;133(5 Suppl 2):1606S-1625S.)

b. Coutsoudis et al. themselves specify that their teachings apply to a very select population of HIV infected women with low vitamin A or on antiretroviral therapy:

> "In conclusion, vitamin A supplementation to a population of HI V infected pregnant women, many of whom had low vitamin A levels, was associated with a decreased number of preterm births. [,..] Vitamin A may be useful in industrial countries to counter the effects of antiretroviral therapy which appears to increase the risk of preterm deliveries."

Thus, it is not obvious that the provision of antioxidants to women who are not chronically depleted and anemic would have a beneficial effect on the treatment of preterm labor or PPROM.

c. **Most importantly**, the teachings of Coutsoudis et al. were not confirmed by others in a similar population when the study design was randomized [Fawzi WW, Msamanga GI, Spiegelman D, Urassa EJ, McGrath N, Mwakagile I), Antelman G, Mbise R, Herrera G, Kapiga S, Willett W, Hunter DJ.Lancei. Randomized trial of effects of vitamin supplements

on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. Lancet 1998 16; 351(9114): 1477-82.]. The absence of confirmation in a randomized trial suggests the conclusion of Coutsoudis as it relates to vitamin A was a false positive result, a result far more common when the conclusion was not what the trial sought to study. Fawzi et al. teach us that multivitamins significantly decrease the incidence of low birth weight, but that when controlled for other nutritional supplements, Vitamin A has no effect on either preterm delivery or birth-weight outcome.

d. From a systematic review of nutritional interventions during pregnancy to prevent poor outcomes including preterm delivery [Villar J, Merialdi M, Gulmezoglu AM, Abalos F, Carroli G, Kulier R, de Onis M. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials, J Nutr. 2003; 133: 1606S-1625S] we learn that the Cochrane review of vitamin A supplementation did not include preterm birth as an outcome. In the large Nepal trial [See Annex Table 1 (ref 63) Trial 92] The overall conclusion is that in well-controlled trials there are no differences in neonatal and infant mortality between the Vitamin A supplemented and placebo groups. Our review of the data from Nepal [Christian P, Khatiy SK, Katz J, Pradhan EK, LeClerq SC, Shrestha SR, Adhikari RK, Sommer A, West KP Jr. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomized community trial. BMJ. 2003 Mar 15;326(7389):571] concludes that in 4926 pregnant women from rural Nepal **none of the supplemental nutritional combinations including Vitamin A reduce the incidence of preterm births.**

In conclusion, the teachings of Coutsoudis et al. even if taken at face value, apply only to the HIV-infected women in Durban, South Africa with significant anemia and low Vitamin A levels. While it may be

inferred from Coutsoudis et al. that Vitamin A and beta-carotene lower the number of preterm deliveries possibly by correcting anemia or other specific nutritional deficiencies in this population, subsequent study strongly suggests their conclusions were not accurate and the result of an inherent study bias. Their teachings on prophylaxis in no way anticipates the present invention where the occurrence of preterm delivery, preterm premature rupture of membranes or outcome of preterm delivery is improved by administration of free radical scavengers irrespective of a correction of nutritional deficiencies or anemia. The Coutsoudis reference is not an effective §102 reference and must be withdrawn.

2. Cherouny:

The examiner rejects claims as being fully anticipated by Cherouny et al. (it appears the correct reference is Biol Reprod 1989 - not AIDS 1999). The examiner feels that by Cherouny teaching that antioxidants inhibit contractile activity that resulted from the presence of hydrogen peroxide that this thus anticipates the present invention. This is a misunderstanding of the teaching of Cherouny. Cherouny is not an effective §102 reference and must be withdrawn.

Cherouny teachings apply to an *in vitro* model where a strip of tissue from the uterus is taken out from the animal, submersed in a solution bubbled with 95% oxygen gas (thus is studied in isolation in an environment characterized by excess oxygen free radical generation) and the contractile force measured. In their paper, they describe spontaneous contractile activity as a normal behavior of the model. This description demonstrates clearly that this model is not applicable to human pregnancy where the uterus inside the pregnant woman does not contract spontaneously under normal conditions. **Thus, teachings based on removal of uterine tissue from an animal (human or rat) cannot be generalized to a whole organism system ("a pregnant animal") as claimed in the present invention.**

In further support of this position, the Applicants observed that pregnancy tissues other than the uterus regulate contractile activity. Experimental evidence from our group [Carvajal JA, Buhimschi IA, Thompson LP, Aguan K, Weiner CP, Chorion releases a factor that inhibits oxytocin-stimulated myometrial

contractility in the pregnant guinea pig. Hum Reprod. 2001 Apr;16(4):638-43.] reveals that placental membranes have an inhibitory activity on uterine contractions maintaining the uterus quiet during pregnancy. Further, it should be noted that fetal membranes contain catalase, an enzyme that physiologically inactivates hydrogen peroxide should it be generated *in vivo*.

Thus Cherouny teaches only that suprapharmacologic oxygen free radical concentrations act *in vitro* as a uterine irritant, and that by decreasing free radical availability *in vitro* by binding the oxygen free radicals with suprapharmacologic concentrations of a free radical trap you may reduce the level of irritation. Because Cherouny lacks multiple elements present *in vivo* and ignores the pharmacologic/physiologic levels of free radical generation that occur *in vivo*, the observations of Cherouny make on spontaneously or peroxide-induced contracting rat uterine strips *ex vivo* cannot fully anticipate the invention is claimed involving a biological organism as a whole, i.e., a pregnant animal. Again, Cherouny is not an effective §102 reference, and must be withdrawn.

3. Barrett:

The examiner rejects claims as being fully anticipated by Barrett et al (mt J Vitam Nutr Res 1994). The examiner feels that Barrett et al. teaches a potential role of the antioxidants Vitamin C and beta carotene in prevention of premature rupture of membranes (PROM). Upon careful review, the Applicants respectfully disagree.

The Barrett study compared amniotic fluid and serum specimens from an experimental group of patients with PROM to a control group with normal pregnancy. The population was 85% black. Of central significance is that the sample of fluid in the control group was obtained directly from the uterus by transabdominal amniocentesis, while the fluid in the PROM group was obtained from the vagina. The latter reflects both vaginal secretions, the amniotic fluid passed through the cervix as it traveled from the uterus, and any metabolic effects upon the fluid as it passed through the cervix or sat in the vagina. **Thus, it is pointed out to the Examiner that the comparison is not between amniotic fluid samples obtained from two**

different groups, but rather a comparison of two different fluid specimens: amniotic fluid from control patients and leaked vaginal fluid in PROM patients. Thus, Barrett does not fully anticipate the present invention, and the §102 rejection must be withdrawn.

The authors of Barrett also point out that "the findings of their study are more representative of the African black females than the whole population. " Further, they note that retinol and alpha-tocopherol concentrations in amniotic fluid and serum are similar. Applicants would respectfully suggest that this finding of similarity does not anticipate the present claims.

Barrett found that women with PROM had lower vaginal fluid ascorbic acid concentrations. However, based on the lack of comparability of the samples analyzed, their results can only teach that the passage of the amniotic fluid into the vagina through the cervix after membrane rupture consumes ascorbic acid. In support of this teaching, we note that it is well known cervical mucus is rich in leukocytes that protect the cervical canal against ascending infections. It is logical to expect leukocytes consume ascorbic acid in their defense, and thus predictable that the concentration of ascorbic acid would decline after exposure of the amniotic fluid to cervical mucus. Moreover, in a separate study in 1991 by the same group [Barrett B, Gunter F, Jenkins J, Wang M. Ascorbic acid concentration in amniotic fluid in late pregnancy. Biol Neonate. 1991;60 (5):333-5.] it was found that

> "...pregnant women who smoked had a significantly lower serum and amniotic fluid ascorbic acid concentration than those who did not smoke. No differences were observed between the groups with or without premature rupture of the fetal membrane. The results suggest that ascorbic acid in the amniotic fluid reflects the ascorbic acid status in the blood of pregnant women and smoking had a greater effect in decreasing the ascorbic acid concentration in amniotic fluid than in serum."

Thus, Barrett's prior work in 1991 suggests that the observation by Barrett in 1993 of a difference ascorbic acid content reflects a lack of comparability of samples, and that their teaching that ascorbic acid may prevent PROM is refuted altogether when controlling for smoking status. The finding that women who

smoke have lower ascorbic acid status than non-smoking women is unrelated to the claims of the present invention.

As it relates to beta-carotene, the levels were not different between PROM and non-PROM patients when controlling for smoking. "However, no difference was observed in serum levels of beta carotene in women who did not smoke." Again Barrett is not an effective §102 reference.

Based on the above arguments, Barrett et al. teaches that women who smoke may have lower ascorbic acid and beta carotene levels in serum and/or amniotic fluid and/or amniotic fluid that leaks through the vagina after rupture of the membranes. Based on the information detailed in our arguments above against Coutsoudis et al. where we note population based supplementation of women has not reduced the preterm delivery rate, it is unlikely that **supplementation** with beta-carotene reduces the occurrence of preterm delivery as presently claimed by the Applicants.

4. Japanese Patent '669:

The examiner rejects claims as being anticipated by the Japanese patent 60197669, which in the examiner's reading teaches the use of a substance that contains vitamin E as a remedy for premature labor. A careful review of the 60197669 Japanese patent indicates rather that it is merely a description of a method to obtain tocopherol (Vitamin E) from a vegetable oil. Although the Japanese reference lists as potential uses for their extracted substance among others "...premature labor and pregnancy disorder, etc," they do not directly provide evidence in support of such a teaching. In fact there is evidence to suggest that administration of tocopherol as a general vitamin supplement to pregnant women not experiencing excess free radical generation will not result in higher tocopherol levels in the neonate and thus it is unlikely to improve the outcome of preterm delivery if it is administered to a such pregnant organism. [Leger CL, Dumontier C, Fouret G, Boulot P, Descomps B. A short-term **supplementation** of pregnant women before delivery does not improve significantly the vitamin E status of neonates--low efficiency of the vitamin E placental transfer. Int J Vitam Nutr Res. 1998;68(5):293-9 (emphasis added)]. Moreover, in a study by Ben-Haroush et al. [Ben-

Haroush A, Harell D, Hod M, Bardin R, Kaplan B, Orvieto R, Bar J. Plasma levels of vitamin E in pregnant women prior to the development of preeclampsia and other hypertensive complications. Gynecol Obstet Invest. 2002;54(1):26-30] plasma levels of Vitamin E were unaltered in women that subsequently developed preterm delivery or other pregnancy complications.

Based on the above, the Applicants believe the 60197669 patent on the method of preparation of tocopherol in no way fully anticipates the presently claimed invention. In particular, claims to the administration of a free radical scavenger to a pregnant animal experiencing excess free radical generation are allowable over the Japanese reference.

CONCLUSION

Further, in light of the Declaration of Irina A. Buhimcshi regarding the §103 reference and in light of the arguments presented regarding the §102 references, the Applicants ask the Examiner to reconsider the claims rejected under §102 and §103, and withdraw his rejection to the newly amended claims.

Further, the Applicants ask the Examiner to review the rewritten allowable claims and indicate their acceptance.

The Applicants ask the Examiner to issue a Notice of Allowance.

Respectfully submitted,
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